Modified Neurosyphilis in the Cape Peninsula

N. JOYCE-CLARKE, A. C. B. MOLTENO

SUMMARY

A prospective study of 148 cases of neurosyphilis revealed that 85 patients exhibited a modified 'forme fruste' of the disease. A high proportion of these patients had evidence of activity in the cerebrospinal fluid, while 6 patients have developed features which are diagnostic of neurosyphilis. During the study a significant number of active seronegative cases were diagnosed and 11 patients have deteriorated on treatment.

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In recent years several authorities have pointed out that cases of neurosyphilis are still common, but that the clinical picture has changed considerably, so that patients present with slight symptoms and subtle clinical signs, and in some cases are seronegative to all tests except the fluorescent treponemal antibody absorption reaction (FTA-ABS).[1-3] The authors' observation of large numbers of patients with lesions suggestive of syphilis but with weakly positive and in some cases negative blood serological reactions suggested that the same change in the pattern of neurosyphilis was far advanced in the Cape Peninsula. In order to assess the virulence of this modified syphilis and the incidence and significance of seronegative cases, the authors set out to investigate the postion.

PATIENTS AND METHODS

Cases were collected from the ophthalmology outpatient department, from the neurology outpatient department, and from the medical wards of Tygerberg Hospital.

Categories of Patients

Group 1: Patients with ocular signs diagnostic of syphilis were referred irrespective of whether blood serological tests were positive or negative. Diagnostic lesions were taken to be: (*a*) fully developed Argyll-Robertson pupils, including the classic, reversed and absolutely rigid pupil variants; (*b*) classic interstitial keratitis, both active and old cases with typical ghost vessels; (*c*) active keratitis pustuliformis profunda.

Group 2: Patients with ocular signs suggestive but not diagnostic of syphilis were also referred, irrespective of whether serological tests were positive or negative. Suspicious lesions were taken to be: (*a*) slight pupillary anomalies — irregularity of outline, inequality, or a dissociation of responses to light and to accommodation; (*b*) optic atrophy with concentric field loss, sheathing of retinal vessels or disseminated retinochoroiditis; (*c*) uveitis.

Group 3: These patients had gross neurological lesions such as paraplegia, hemiplegia and epilepsy with positive serological tests.

Group 4: The control group consisted of patients without clinical signs but with positive blood serology.

Evaluation of Cases

All patients underwent full neurological and ophthalmological examinations which included the following special investigations: (*i*) Wassermann reaction (WR), rapid plasma reagin test (RPR), VDRL (these were reagin reactions), and FTA-ABS tests;[4] (*ii*) white blood cell count, haemoglobin and erythrocyte sedimentation rate estimations; (*iii*) liver function tests and serum protein electrophoresis; (*iv*) lumbar puncture at the initial examination and, if the fluid was in any way abnormal, repeated tests every 4 - 6 months until fluid became normal.

The cerebrospinal fluid (CSF) was examined chemically and microscopically by the routine diagnostic laboratories for cells, protein content, and presence of globulins, sugar and chlorides. Specific antibodies were tested for by the WR, VDRL, RPR and FTA-ABS tests, which were done as a routine on all fluids.

Diagnosis

Diagnosis was based on clinical signs and symptoms, while activity was assessed by the CSF abnormalities. When there was doubt or when response to treatment was unsatisfactory, patients were fully evaluated by electroencephalography (EEG), brain scan, air encephalography and angiography to exclude alternative disease as far as possible.

Therapy

Penicillin therapy was given to all patients who had active disease and was used as a diagnostic aid in doubtful and seronegative cases. All treated patients received a minimum of 4,8 million units of a combination of sodium-, procaine- and benzathine-penicillin intramuscularly weekly for 10 weeks (sodium penicillin 1 200 000 U, procaine penicillin 1 200 000 U, benzathine penicillin 2 400 000 U).

Follow-up Examination

After the initial examination all patients were re-examined every 3 - 6 months to assess response to treatment and to detect the development of fresh clinical signs.

Departments of Medicine and Ophthalmology, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

N. JOYCE-CLARKE, M.B. B.CH., M.R.C.P.
A. C. B. MOLTENO, M.B. CH.B., F.R.C.S.

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RESULTS

During a period of 24 months, 168 patients were seen and evaluated; 148 were diagnosed as having definite signs of syphilis. The syphilitic patients fell into the following groups:

Group A: Patients with a lesion diagnostic of syphilis and at least the FTA-ABS reaction positive (46 cases).

Group B: Patients with a diagnostic lesion but with all blood tests (including the FTA-ABS test) negative (5 cases).

Group C: Patients with suspicious lesions only but with at least the FTA-ABS test positive (77 cases).

Group D: Patients with suspicious lesions but with all tests (including the FTA-ABS reaction) negative (8 cases).

Group E: Patients with gross nonspecific neurological lesions (paraplegia, epilepsy or hemiplegia) and with at least the FTA-ABS reaction positive (12 cases).

Group F: Controls without lesions or symptoms but with positive blood serological tests (20 cases).

The majority of patients were in group C or D and presented with suspicious lesions, either slight pupillary anomalies (47), optic atrophy (27) or uveitis (21). The question remained whether these 'mild', inconspicuous signs were evidence of active syphilis or not. Analysis of the CSF protein levels with the Student *t* test demonstrates that there is less than a 0,001 chance that the 77 patients with suspicious lesions but with positive blood tests belong to the same population as the 20 controls. Furthermore, the 8 patients with suspicious lesions and negative blood tests had a higher mean CSF protein level than similar patients with positive tests (Table I). CSF protein levels are normally between 5 and 40 mg/100 ml and the majority of the control group values fell well within this range. However, in many patients with suspicious or diagnostic lesions, borderline CSF protein values were found. The significance of these values was demonstrated by repeat examination of CSF 6 months after completion of a course of 10 weekly injections of 4,8 million units of a combination of sodium-, procaine- and benzathine-penicillin, when a fall in CSF protein values was found in 19 out of 22 patients (Table II).

Failure to Respond to Penicillin Therapy

Eleven patients deteriorated after treatment with penicillin; 7 of them were originally placed in the group with suspicious lesions. In 2 of these patients, deterioration has been limited to the gradual development of classic Argyll-Robertson pupil responses. However, in the remaining 5 patients, multiple lesions developed during the succeeding 2 years, with severe disability. Failure to respond to treatment has been consistently associated with persistence or increase of raised CSF protein levels, and 5 out of 7 patients now have signs that are virtually pathognomonic of neurosyphilis (Table III).

Four more patients in the group with diagnostic lesions and positive serum tests have deteriorated significantly after treatment with penicillin, while 17 patients, diagnosed

TABLE II. CSF PROTEIN LEVELS BEFORE AND AFTER PENICILLIN TREATMENT IN 22 PATIENTS

	CSF protein (mg/100 ml)		
	Before treatment	After trea ment	Difference
Diagnostic lesions — positive serology	42	40	− 2
	36	28	− 8
	38	22	−16
	40	33	− 7
Diagnostic lesions — negative serology	47	28	−19
	46	28	−18
Suspicious lesions — positive serology	52	52	− 0
	48	26	−24
	44	34	−10
	40	30	−10
	26	20	− 6
	52	24	−28
	42	72	+30
	44	30	−14
	31	40	+ 9
	32	24	− 8
	30	20	−10
	42	40	− 2
	36	41	+ 5
Suspicious lesions — negative serology	44	31	−13
	58	50	− 8
	56	42	−14

TABLE I. RESULTS OF SEROLOGICAL TESTS, CSF PROTEIN ESTIMATIONS AND CSF FTA-ABS TESTS IN 168 PATIENTS

Diagnostic group	Serological tests: All 4 tests positive	Serological tests: Only FTA - ABS positive	CSF protein (mg/100 ml): Range	Mean	SD	CSF FTA - ABS-positive
Group A (46 cases)	16	7	14 - 102	41	17,6	11
Group B (5 cases)	—	—	22 - 52	39,4	11,4	—
Group C (77 cases)	31	13	20 - 98	42	17,6	16
Group D (8 cases)	—	—	8 - 58	47	17,5	1
Group E (12 cases)	11	1	24 - 128	50	8,5	5
Group F (20 cases)	5	9	18 - 52	28	9,3	2

TABLE III. PATIENTS WITH SUSPICIOUS LESIONS WHO DETERIORATED ON TREATMENT

Patient	Initial lesion	Initial CSF protein (mg/100 ml)	Penicillin dosage	Current clinical state	Present CSF protein (mg/100 ml)	Number of relapses
1	Suspicious pupil response	36	48 mill. U	Fully developed Argyll-Robertson pupil	41	0
2	Suspicious pupil response	31	48 mill. U	Fully developed Argyll-Robertson pupil	40	0
3	Peripheral choroiditis, hemiplegia	47	1 800 mill. U	Argyll-Robertson pupils, optic atrophy, epilepsy, left hemiplegia, demented +++	72	4
4	Left central retinochoroiditis	42	700 mill. U	Argyll-Robertson pupils, early optic atrophy, classic features of tabo-paresis, demented +	42	3
5	Suspicious pupil response	57	95 mill. U	Argyll-Robertson pupils, early optic atrophy, demented ++	59	2
6	Uveitis	55	340 mill. U	Blind from vitreous haemorrhage due to retinal vasculitis, Jacksonian epilepsy	55	1
7	Uveitis	67	96 mill. U	Blind from acute optic atrophy, demented +	50	1

by the authors as having *active* neurosyphilis, have hospital records which show that they had received adequate treatment with penicillin less than 5 years previously (6 weekly injections of 2,4 million units of a combination of sodium-, procaine- and benzathine-penicillin).

So far none of the 13 seronegative patients has shown clinical deterioration after treatment.

False Negative Serological Tests

The incidence of false negative serological reactions is set out in Table IV. From the Table it is clear that the WR is virtually useless in these cases, that the VDRL and RPR tests are falsely negative in 1 case out of 4, and that the FTA-ABS reaction is falsely negative in 1 case out of 12.

The findings can be summarized thus: a large number of patients were seen with subtle clinical signs suggesting neurosyphilis; these signs involved mainly the eyes, cranial nerves or brain, and they were accompanied in some patients by raised, borderline or normal protein levels in the CSF, but on the whole the CSF protein level was elevated to a highly significant degree in the group with signs. Five out of 85 patients in this group have developed 'diagnostic' signs of neurosyphilis during the past 2 years. The FTA-ABS reaction was positive in 77 out of 85 patients.

Treatment with penicillin lowered the CSF protein level in the majority of patients (even borderline or apparently normal values) (Table II).

Diagnostic Features

The most reliable and consistently helpful diagnostic features were: abnormal pupil reflexes, the FTA-ABS reaction and elevation of CSF protein levels. CSF serology and the CSF cell count were far less reliable, but still very useful as indices, while haematological tests and liver function tests were of no value in diagnosis.

DISCUSSION

The major difficulty associated with accepting the concept of a modified form of neurosyphilis associated with

TABLE IV. INCIDENCE OF FALSE NEGATIVE SEROLOGICAL TESTS

Tests done	Diagnostic lesions (49)	Suspicious lesions (85)	Gross lesions (12)	Total (%)
FTA (149)	5 (3 abnormal CSF*)	8 (4 abnormal CSF)	0	8,7
RPR (149)	12 (5 abnormal CSF)	21 (10 abnormal CSF)	1	22,8
VDRL (149)	12 (5 abnormal CSF)	25 (13 abnormal CSF)	1	25,0
WR (149)	32 (13 abnormal CSF)	48 (24 abnormal CSF)	2 (1 abnormal CSF)	55,0

* Abnormal CSF = protein 41 mg/100 ml.

subtle clinical signs and a high incidence of false negative serological reactions is simply this: if signs are subtle and serology is negative, how can one make a diagnosis of syphilis? Furthermore, even if the patient has syphilis, is this not a burnt-out inactive infection? We think so, and maintain that in an *individual* patient, suspicious clinical signs, a borderline or raised level of CSF protein and a positive serological test do not necessarily indicate active syphilis. Unfortunately, recent studies of seronegative syphilis[3,4] have depended for diagnosis on the use of one of the more specific and sensitive tests, and therefore the diagnosis in *totally* seronegative patients with subtle signs would have been missed. (The *Treponema pallidum* immobilization (TPI) test is not performed in the Cape, and while it is possible that some of our seronegative patients are TPI-positive, they are seronegative from the point of view of practical clinical diagnosis.) We designed this project specifically to overcome this difficulty by adopting as a minimum requirement for the diagnosis of neurosyphilis the simultaneous presence of 3 of the following criteria: (*i*) 'diagnostic' or 'suspicious' clinical signs; (*ii*) a significant elevation of CSF protein; (*iii*) a significant fall in CSF protein on treatment with penicillin (even if later followed by a relapse); (*iv*) positive serological tests in the CSF.

The use of a control series of patients without any clinical signs but with positive blood reactions demonstrated that both the group with diagnostic and that with suspicious clinical signs were associated with a highly significant elevation in CSF protein levels, while follow-up examination of the CSF of patients after treatment revealed a marked tendency for borderline or apparently normal CSF protein levels to fall (Table II).

These findings taken together indicate that the majority of the patients were suffering from neurosyphilis, as there is no other common neurological disease which exhibits syphilis-like clinical signs, elevated CSF protein, and a reduction in protein levels on treatment with penicillin.

Included in the groups with 'diagnostic' and 'suspicious' lesions are two subgroups of particular interest. A group of 13 patients with totally negative blood reactions (in these cases tests were repeated once on a separate blood specimen before the case was classed as seronegative). The diagnosis in this group depended only on clinical signs, elevated CSF protein, and a lowering of the protein levels on penicillin treatment. One of these patients had a positive FTA-ABS reaction in the CSF, a somewhat unexpected finding which has, however, been described previously.[5] The difficulty of diagnosing seronegative cases is borne out by the higher levels of CSF protein in these patients, probably because, in the absence of positive serological tests, patients had advanced disease, with more marked physical signs, before syphilis was considered as a diagnosis.

The other group consisted of 11 patients who did not respond satisfactorily to treatment. They were intensively investigated to exclude alternative disease, but so far no credible alternative diagnosis has been made in any of these patients. They were detected when follow-up lumbar puncture 3 months after they had completed a course of 10 weekly injections of penicillin indicated that the CSF had not reverted to normal or had deteriorated chemically or cytologically. Others were identified by the appearance of fresh lesions during and after treatment. These patients were closely followed and it was found that systemic steroids had no influence on the disease, and that intensive and prolonged treatment with penicillin had caused the CSF chemical values to change towards normal, but that relapse followed within a few weeks to months after penicillin treatment was stopped. Repeated courses of penicillin produced the same cycle of changes (Table III). It is too early to be sure of the outcome in these patients, and whether or not the progress of the disease will ultimately be arrested, but so far 3 patients out of 7 who originally presented with 'suspicious' signs have become seriously demented and had to be given a pension or sheltered employment, while 1 patient has become totally blind.

The overall picture that emerges is that the majority of patients with neurosyphilis present with subtle clinical signs and with weakly positive or even negative serology; furthermore, while a course of 48 million units of penicillin over 10 weeks cures the majority of patients, it is ineffective in at least 7% of cases.

The reasons for this state of affairs are obscure, but it is well known that inadequate treatment of syphilis during the early stages can produce seronegative *'formes frustes'* of the disease. Antibiotics, including penicillin, are used on an enormous scale, and many cases of syphilis must be masked by fortuitous administration of antibiotics for other conditions, while we have in fact observed spectacular Herxheimer reactions after penicillin injections given incidentally for the treatment of other conditions. A more certain consequence of administering inadequate doses of penicillin to people with syphilis is illustrated by 2 patients who received respectively two and three injections of 4,8 million units of long-acting penicillin before they absconded from further treatment. The first patient reappeared 2 months later with acute optic neuritis, vomiting and headache. She was treated with massive doses of penicillin and steroids, but her level of consciousness deteriorated; she underwent ventricular drainage which relieved her symptoms and produced CSF with a positive FTA-ABS reaction. This woman's disease gradually became inactive, leaving her totally blind, with a moderate degree of mental impairment. The second patient, a young man, had a similar course; inadequate treatment for a left-sided syphilitic uveitis was followed by a bilateral uveitis with rapidly progressive involvement of the nervous system leading to almost total blindness and grand mal epilepsy. The full clinical picture developed relentlessly over 3 months, while the patient was hospitalized and received penicillin and prednisone in high doses. These 2 patients exhibited the classic accelerated development of neurosyphilis, which was said to occur after inadequate treatment with arsenicals; however, in the present 2 cases 'inadequate treatment' meant 9 million and 14 million units of long-acting penicillin, respectively. The

tragic outcome in these cases emphasizes the need to take syphilis seriously, to diagnose neurological involvement by routine lumbar puncture, to treat energetically until the CSF becomes normal, and to detect relapses early by follow-up examination of the CSF in exactly the same way as was necessary before the introduction of penicillin, when arsenicals were the only available form of treatment.

REFERENCES

1. Smith, J. L. (1969): *Spirochaetes in Late Seronegative Syphilis, Penicillin Notwithstanding*. Springfield, Ill.: Charles C. Thomas.
2. Hooshmand, H., Escobar, M. R. and Kopf, S. W. (1972): J. Amer. med Ass., **219**, 726.
3. Jaffe, H. W. (1975): Ann. intern. med., **83**, 846.
4. Deacon, W. E., Lucas, J. B. and Price, E. V. (1966): J. Amer. med. Ass., **198**, 624.
5. Brain, W. R. (1962): *Diseases of the Nervous System*, 6th ed., pp. 386 - 387. London: Oxford University Press.

Myeloid Leukaemoid Reactions in South African Blacks

LORNA G. MACDOUGALL, BARBARA STRICKWOLD

SUMMARY

Myeloid leukaemoid reactions were observed in 18 Black adults and 20 Black children at Baragwanath Hospital, Johannesburg, during a 10-month period. This represented an incidence of 1,3/1 000 adult medical admissions and 3,7/1 000 paediatric medical admissions. During the same period the incidence of myeloid leukaemoid reactions in White children in Johannesburg and in Black and White children in Buffalo, NY, was less than 1/1 000 admissions. The reactions were associated with bacterial infections, neoplasms, hepatorenal failure, acute metabolic disorders and non-malignant blood dyscrasias. The mortality in adults was 55,6% and in children 35%. Sixty-five per cent of all deaths occurred within 24 - 48 hours of admission. Residual morbidity in survivors was common. The pattern of acute leukaemia in the same hospital population is predominantly myelocytic in both adults and children.

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Leukaemoid reactions are generally considered to occur infrequently[1] and the majority have been recorded as single case reports and are mainly myeloid in type. The true incidence is therefore difficult to assess. Kitamura and associates[2] reported that 134 leukaemoid reactions had been notified in Japan between 1923 and 1958. More recently a high incidence of leukaemoid reactions (9,1%) was associated with an epidemic of shigellosis which affected 566 patients in Bangladesh.[3] Two series of paediatric patients with leukaemoid reactions have also been reported[4,5] and it is thought that such reactions are more common in children than in adults.

In this article we wish to draw attention to the apparent frequency with which leukaemoid reactions occur in South African Blacks in Johannesburg and to discuss the possible significance.

PATIENTS AND METHODS

The study was conducted over a 10-month period and included adults and children (aged 0 - 15 years) admitted to the medical, paediatric and intensive care wards of Baragwanath Hospital, a 2 000-bed general hospital with approximately 16 500 adult and 6 500 paediatric medical admissions per year. The criteria used for diagnosis of leukaemoid reactions were those of Hill and Duncan[6] and Holland and Mauer,[4] namely a total white blood cell count (WBC) of 50 000/μl or more, and/or the presence of immature cells, capable of division, in the peripheral blood.

Haemoglobin concentration and red and white blood cell counts were estimated on a Coulter Counter Model S-Senior. White cell counts in excess of 56 000/μl were recounted manually with a Neubauer counting chamber. Platelet counts were estimated on a Coulter Thrombocyte Counter-C. Blood films were stained in an Ames Hema-

Metabolic and Nutrition Research Unit, Department of Paediatrics, University of the Witwatersrand and Baragwanath Hospital, Johannesburg

LORNA G. MACDOUGALL, M.B. CH.B., D.C.H.
BARBARA STRICKWOLD, M.T.

Date received: 19 April 1977.
Reprint requests to: Dr L. Macdougall, Metabolic Unit, Baragwanath Hospital, PO Bertsham, 2013 RSA.